

# Anti-tRNA synthetase syndrome interstitial lung disease: A single center experience

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## ABSTRACT

**Background:** Recognition of Anti-tRNA synthetase (ARS) related interstitial lung disease (ILD) is key to ensuring patients have prompt access to immunosuppressive therapies. The purpose of this retrospective cohort study was to identify factors that may delay recognition of ARS-ILD.

**Methods:** Patients seen at Vanderbilt University Medical Center between 9/17/2017-10/31/2018 were included in this observational cohort. Clinical and laboratory features were obtained via chart abstraction. Kruskal-Wallis ANOVA, Mann-Whitney U, and Fisher's exact t tests were utilized to determine statistical significance.

**Results:** Patients with ARS were found to have ILD in 51.9% of cases, which was comparable to the frequency of ILD in systemic sclerosis (59.5%). The severity of FVC reduction in ARS (53.2%) was comparable to diffuse cutaneous systemic sclerosis (56.8%,  $p = 0.48$ ) and greater than dermatomyositis (66.9%,  $p = 0.005$ ) or limited cutaneous systemic sclerosis (71.8%,  $p = 0.005$ ). Frank honeycombing was seen with ARS antibodies but not other myositis autoantibodies. ARS patients were more likely to first present to a pulmonary provider in a tertiary care setting (53.6%), likely due to fewer extrapulmonary manifestations. Only 33% of ARS-ILD were anti-nuclear antibody, rheumatoid factor, or anti-cyclic citrullinated peptide positive. Patients with ARS-ILD had a two-fold longer median time to diagnosis compared to other myositis-ILD patients (11.0 months, IQR 8.5–43 months vs. 5.0 months, IQR 3.0–9.0 months,  $p = 0.003$ ).

**Conclusions:** ARS patients without prominent extra-pulmonary manifestations are at high risk for not being recognized as having a connective tissue disease related ILD and miscategorized as usual interstitial pneumonia/idiopathic pulmonary fibrosis without comprehensive serologies.

## 1. Introduction

Recognition of IIM spectrum disease is challenging due to phenotypic heterogeneity. While the original Bohan and Peter criteria focused on classic skin rashes and muscle weakness [1], there has been increasing recognition that these clinical classifications oversimplify marked heterogeneity and that myositis autoantibodies are associated with a variety of classical clinical presentations (supplemental table 1). ILD is particularly prevalent in the ARS, which classically presents with the triad of arthritis, interstitial lung disease, and mechanic's hands. Amongst ARS antibodies, however, the frequency of skin, muscle, and

lung disease is variable. Patients with anti-Jo-1 antibodies are more likely to have joint and muscle involvement; non-Jo-1 positive patients are more likely to have vascular and cutaneous involvement [2]. Patients with anti-PL7 and anti-PL12 antibodies have more severe pulmonary manifestations [3].

The diagnosis of IIM-ILD remains a challenge. Presently, the American Thoracic Society recommends that CTD-ILD be ruled out clinically and with basic serologic screening (ANA, RF, and CCP), but does not recommend comprehensive myositis serologies [4]. However, not only are basic serologies more apt to be negative in IIM compared to other connective tissue diseases, but IIM patients are also less likely to fulfil clinical CTD classification criteria. For example, nearly all patients with

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**Abbreviations**

ANA	anti-nuclear antibody
ACR	American College of Rheumatology
ARS	anti-tRNA synthetase syndrome
CCP	anti-cyclic citrillinated peptide
CLASS	classification criteria of antisynthetase syndromes
CTD-ILD	connective tissue disease related interstitial lung disease
CK	creatine kinase
dcSSc	diffuse cutaneous systemic sclerosis
DLCO	diffusion capacity of the lung for carbon monoxide
DM	dermatomyositis
EULAR	European League Against Rheumatism
FVC	forced vital capacity
GERD	gastroesophageal reflux disease

IAIMC	ILD in autoimmune inflammatory myopathy cohort
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IQR	interquartile range
lcSSc	limited cutaneous systemic sclerosis
MYSTIC	myositis and scleroderma treatment initiative center
PFT	pulmonary function tests
PM	polymyositis
RF	rheumatoid factor
RHC	right heart catheterization
RVSP	right ventricular systolic pressure
SSc	systemic sclerosis
UIP	usual interstitial pneumonia
VUMC	Vanderbilt University Medical Center

SSc-ILD will have a positive ANA, and the clinical classification criteria for SSc have >95% sensitivity in external validation cohorts [5]. In contrast, fewer than 50% of ARS patients have a positive ANA [6], and external validation of the 2017 ACR/EULAR classification criteria for IIM cohorts has yielded sensitivities as low as 71% [7]. For non-Jo1 associated ARS, the sensitivity of the 2017 ACR/EULAR classification criteria is as low as 25% [8]. This low sensitivity has led to the ACR/EULAR funding the CLASS project to develop improved criteria to diagnose of ARS [9].

The goal of this retrospective cohort study was to (1) evaluate the clinical, radiographic, and serologic features of ARS compared to other patients with IIM and SSc, and (2) gain insights into possible etiologies leading to delayed diagnosis and therapy in the ARS subgroup. We hypothesize that ARS patients will have more subtle clinical and laboratory findings compared to other subsets of IIM-ILD and SSc-ILD despite an equivalent physiologic severity of ILD.

## 2. Patients and methods

### 2.1. Patient identification

Institutional Review Board approval was obtained. Patients were identified from either the MYSTIC cohort or IAIMC. Patients with suspected systemic sclerosis, idiopathic inflammatory myopathies, mixed connective tissue disease, or interstitial pneumonia with autoimmune features were eligible for referral to the MYSTIC cohort by their treating provider in the outpatient pulmonary, thoracic surgery, or rheumatology clinic, the inpatient rheumatology or pulmonary consulting service, or by their critical care provider in the intensive care unit (VUMC IRB 141415) from September 20, 2017–December 31, 2019. As MYSTIC is a longitudinal convenience cohort, IAIMC subjects were identified through the electronic medical record (VUMC IRB 180672) using a keyword search of the following: “dermatomyositis”, “polymyositis”, “anti-synthetase syndrome”, “systemic sclerosis” in any Vanderbilt Rheumatology or Pulmonology affiliated practice visit between July 1, 2018–October 31, 2018. Myositis attributed to medications, infection, or another rheumatologic condition (e.g. mixed connective tissue disease). Diagnoses were verified by review of progress notes, laboratory findings, and scanned documents.

### 2.2. Clinical phenotyping

Clinical phenotyping was performed by chart abstraction to identify date of symptom onset, skin manifestations (digital ulceration/pitting, mechanic’s hands, Gottron’s sign/papules, heliotrope rash, shawl sign, skin ulcerations), Raynaud’s phenomenon, inflammatory arthritis, pulmonary manifestations (ILD, pulmonary arterial hypertension),

myocarditis, muscle weakness, esophageal dysmotility and/or reflux. Serologic data collected included immunofluorescence ANA titer and pattern (speckled, smooth, nucleolar, centromere), RF, anti-CCP, and comprehensive myositis serologies (Jo-1, PL-7, PL-12, EJ, OJ, SRP, Mi-2, P155/140, Tif-1γ, SAE1, MDA-5, NXP-2, Ro52, Ro60, Pm/Sc1-100, U3RNP, U2RNP through ARUP, Salt Lake, UT). Data on cytoplasmic ANA antibodies was not routinely available. Laboratory values for CK were recorded when available. Patients with DM or PM met the 2017 ACR/EULAR classification criteria for probable or definite DM or PM [10] using the online calculator (<http://www.imm.ki.se/biostatistics/calculators/iim/>). Patient with ARS met the diagnostic criteria proposed by Connors et al. [11] but were not required to meet the 2017 ACR/EULAR classification criteria. SSc patients met the 2013 classification criteria [12]. When documenting first point of contact at VUMC, patients presenting to thoracic surgery were classified as having presented to a pulmonary provider. Basic demographic data such as age, self-identified gender, and self-identified race/ethnicity were also collected.

### 2.3. Pulmonary phenotyping

Pulmonary phenotyping was performed using chart abstraction and analysis of CT scan reports, chest x-ray, PFTs, echocardiogram, RHC, and pathology reports. Patients were classified as having interstitial lung disease if the radiologist reading the clinical CT scan determined that fibrosis or interstitial lung disease was present on CT scan or chest x-ray if CT was unavailable. The severity of restriction or reduction in DLCO was graded as mild (65–79% predicted), moderate (50–64% predicted) or severe (<50% predicted) using the worst available PFT value. Patients were classified as having PH if an echocardiogram demonstrated RVSP >40 mmHg or mean pulmonary artery pressure on RHC >20 mmHg [13]. RHC was considered gold standard in cases of conflicting data. Clinical CT reports were analyzed for mention of honeycombing, bronchiectasis, or ground glass opacities; imaging was not overread by a thoracic radiologist. Determinations of UIP by the reading radiologist were also recorded.

### 2.4. Statistics

All available cases were analyzed. Bias was minimized through blinding during chart abstractions. Missing data was addressed through pairwise deletion. Categorical variables were analyzed using Fisher’s exact test through the GraphPad Quick Calcs Web site: <http://www.graphpad.com/quickcalcs/> (accessed November 2020). Differences in continuous variables were tested using Kruskal-Wallis ANOVA for multiple comparisons followed by Mann-Whitney U tests for comparisons between groups in GraphPad Prism v.7.04. All analyses were two-tailed, and *p* values of less than 0.05 were considered statistically

significant. Data is reported as the average  $\pm$  standard error of the mean unless otherwise noted.

### 3. Results

#### 3.1. Demographics

Demographic characteristics are shown in Table 1. One hundred twenty-five patients were included in the study; one patient was excluded due to conflicting historical reports regarding the presence of ILD and the lack of any PFTs or CT scans. Eighty-four patients (20 DM, 4 PM, 16 ARS, 14 dcSSc, 30 lcSSc) were included from the prospective MYSTIC cohort; 40 unique patients were included from electronic IAIMC cohort (17 DM, 8 PM, 12 ARS, 2 dcSSc, 1 lcSSc). Subjects were predominantly female (77.9% IIM, 78.7% SSc) and Caucasian (81.8% IIM, 78.7% SSc). Median disease duration was estimated from the first report of symptom onset to cohort enrollment and was 5.2 years for IIM versus 9.5 years in SSc ( $p = 0.007$ ).

#### 3.2. Clinical phenotypes in IIM

Clinical characteristics of IIM patients are shown in Table 2. Thirty-seven patients (48.1%) were classified as DM, and 12 (15.5%) were classified as PM. Twenty-eight (36.4%) were diagnosed as ARS. Subjective proximal muscle weakness was less common in ARS (64.3%) than PM (100%,  $p = 0.002$ ) but not DM (73.0%,  $p = 0.09$ ). There was no difference in the frequency of CK elevation in ARS (75.0%) compared to DM (78.3%,  $p = 0.77$ ) or PM (91.7%,  $p = 0.40$ ). Dysphagia or GERD was present in 46.4% of ARS patients, which was not statistically different from DM (29.8%,  $p = 0.20$ ) or PM (66.7%,  $p = 0.31$ ). Inflammatory arthritis was noted in 60.7% of ARS patients, which is higher than either DM (27.0%,  $p = 0.01$ ) or PM (8.3%,  $p = 0.004$ ). By convention, cutaneous manifestations are absent in polymyositis. There was a lower prevalence of Gottron's sign/papules or heliotrope rash in ARS compared to DM (21.4% v. 89.1%,  $p = 0.0001$ ). There was no difference in prevalence between ARS and DM of mechanic's hands (43.8% v.

24.3%,  $p = 0.18$ ) or Raynaud's phenomenon (37.8% v. 35.7%,  $p = 1.0$ ).

Known interstitial lung disease was present in 51.9% of IIM patients. Chest CT scans were available for all but two IIM-ILD patients. ILD was more frequently seen in ARS (78.5%) than in dermatomyositis (40.5%,  $p = 0.00263$ ) or polymyositis (25.0%,  $p = 0.003$ ). In this cohort, all patients with PL-7, PL-12, or EJ antibodies had interstitial lung disease; 80% of Jo-1 positive patients had ILD. Patients with Mi-2 associated dermatomyositis had the lowest frequency of ILD with only 20.0% having known ILD.

Serologically, only 36% of ARS patients were ANA positive compared to 80.6% of DM patients ( $p = 0.004$ ) and 60% of PM patients ( $p = 0.45$ ). Ro52 positivity was observed with similar frequency in ARS and DM (63.6% v. 40.0%,  $p = 1.00$ ) but no PM patient was Ro52 positive. There was no statistically significant difference in the frequency of RF positivity.

#### 3.3. Patients with ARS-ILD frequently present to pulmonary providers at a tertiary center

Of ARS patients, 53.6% presented first to pulmonary providers, which is significantly higher than DM (16.2%,  $p = 0.003$ ) or PM (8.3%,  $p = 0.01$ ). There was no difference in the likelihood of Jo-1 or non-Jo1 associated ARS to present first to a pulmonary provider (60.0% v. 75.0%,  $p = 0.65$ ). Of the 15 patients with ARS-ILD who presented initially to pulmonology, 80% of patients had been seen by outside pulmonologists and 40% by outside rheumatologists. Only one had received the correct diagnosis of ARS-ILD prior to tertiary referral. Three ARS patients were diagnosed with idiopathic pulmonary fibrosis (IPF) prior to referral, and seven others were suspected to have some other CTD-ILD. One of the three patients with a prior diagnosis of IPF had a CT read of UIP. The time from symptom onset to diagnosis could be abstracted for 21/22 ARS-ILD patients, 11/15 DM-ILD patients, and 3/3 PM-ILD patients. Patients with ARS-ILD had a longer median time to diagnosis (11.0 months, IQR 8.5–43 months) than other IIM-ILD subsets (5.0 months, IQR 3.0 to 9.0,  $p = 0.003$ ) (Fig. 1). There was a trend towards ARS-ILD patients presenting to pulmonary clinic being less likely to meet IIM classification criteria, but this did not reach significance (66.7% v. 85.8%,  $p = 0.6158$ ). The only significant association with delayed diagnosis was younger age. However, we cannot exclude that other clinical features may have been identified in a larger sample (supplemental table 2).

While many 2018 ATS guideline panelists advocated for sending a myositis panel as part of the ILD evaluation, only ANA, RF, and CCP were included in the final recommendations [4]. Even at another tertiary ILD center, a myositis panel was not sent at first opportunity in 12.1% of cases [14]. We next sought to evaluate the efficacy of detecting a potential CTD-ILD with a basic serologic assessment using ANA, RF, and anti-CCP testing (Table 3). Patients with ARS-ILD were much less likely to be identified using this strategy than DM-ILD (33.3% v. 86.7%,  $p = 0.002$ ). If a CK was also obtained, the likelihood of detecting a possible CTD-ILD increased to 72.7% for ARS-ILD compared to 86.7% for DM-ILD ( $p = 0.43$ ). Statistical comparisons to PM-ILD were precluded due to small sample size. Myositis specific serologies were required to detect the final 27.3% of patients with ARS-ILD.

#### 3.4. Radiographic features of ARS-ILD

Radiographic features of IIM and SSc associated ILD are shown in Table 4. Due to the paucity of PM-ILD, these were excluded from statistical comparisons. Notably, only patients with anti-tRNA synthetase antibodies (22.7%) had CT scans that were read by a radiologist as compatible with UIP; no patient a non-anti-tRNA synthetase antibody had a CT scan compatible with UIP. The solitary patient with clinical dermatomyositis and a UIP pattern CT scan did not have comprehensive myositis serologies. Patients with UIP pattern CT scans ranged in age from 49.2 to 70.8 years of age and there was a trend towards the median

**Table 1**  
Demographics.

	Idiopathic Inflammatory Myopathies (n = 77)	Systemic Sclerosis (n = 47)	p value
<b>Age (years)<sup>a</sup></b>	57.7 (48.4,66.7)	62.3 (52.3,69.0)	.013
<b>Female Gender</b>	60 (77.9%)	37 (78.7%)	1.00
<b>Race</b>			
Caucasian	63 (81.8%)	37 (78.7%)	0.82
African American	11 (14.2%)	7 (14.9%)	1.00
Other	3 (3.9%)	3 (6.4%)	0.67
<b>Disease Duration (years)<sup>a</sup></b>	5.2 (2.4,10.4)	9.5 (4.8,14.6)	0.007
<b>Known Presence of ILD</b>	40 (51.9%)	28 (59.5%)	0.46
Radiographic and physiologic evidence of ILD	33/40 (82.5%)	20/28 (71.4%)	0.37
Radiographic evidence of ILD with normal PFTs	2/40 (5.0%)	1/28 (3.6%)	1.00
Physiologic evidence of ILD with normal imaging	5/40 (12.5%)	6/28 (21.4%)	0.34
Historic documentation without objective data	0/40	1/28 (3.6%)	1.00
<b>Known Presence of Pulmonary Hypertension</b>	8 (20%)	17 (36.1%)	0.001
<b>Pulmonology as First Point of Care at VUMC</b>	22 (28.5%)	13 (27.6%)	1.00

Abbreviations: ILD = interstitial lung disease, PFTs = pulmonary function tests, VUMC=Vanderbilt University Medical Center.

<sup>a</sup> Reported as median (interquartile range).

**Table 2**  
Clinical phenotype of idiopathic inflammatory myopathies patients<sup>a</sup>.

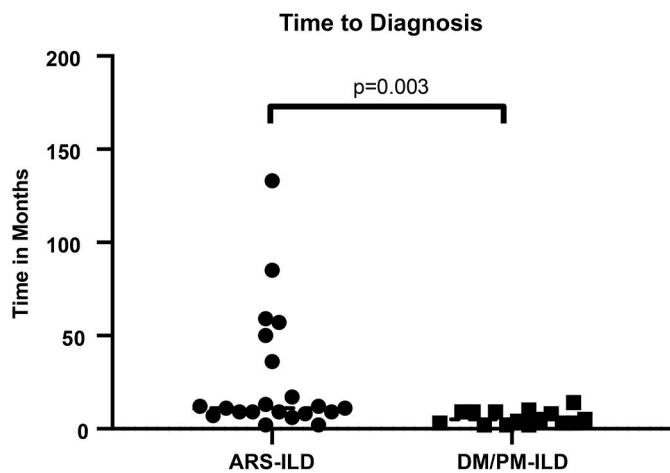
	Associated Serologies			Cutaneous Manifestations <sup>b</sup>		Muscle Involvement		Arthritis	Dysphagia or GERD	Raynaud's Phenomenon
	ANA	RF	Ro52	Gotttron's or Heliotrope Rash	Mechanic's Hands	Proximal Muscle Weakness	CK Elevation			
By Clinical Phenotype <sup>c</sup>										
Dermatomyositis (n = 37)	25/31 (80.6%)	4/17 (23.5%)	8/12 (40.0%)	33/37 (89.1%)	9/37 (24.3%)	27/37 (73.0%)	29/37 (78.3%)	10/37 (27.0%)	11/37 (29.8%)	14/37 (37.8%)
Polymyositis (n = 12)	6/10 (60.0%)	2/5 (40.0%)	0/6 (0%)	0/12 (0%)	0/12 (0%)	12/12 (100%)	11/12 (91.7%)	1/12 (8.3%)	8/12 (66.7%)	2/12 (16.7%)
Anti-Synthetase Syndrome (n = 28)	9/25 (36.0%)	4/21 (19.0%)	14/22 (63.6%)	6/28 (21.4%)	12/28 (43.8%)	18/28 (64.3%)	21/28 (75.0%)	17/28 (60.7%)	13/28 (46.4%)	10/28 (35.7%)
By Serology										
Jo-1 (n = 14)	3/11 (27.2%)	2/10 (20%)	5/9 (55.6%)	2/14 (14.3%)	8/14 (57.1%)	12/14 (85.6%)	12/14 (85.6%)	13/14 (92.9%)	7/14 (50%)	6/14 (42.9%)
PL-7 (n = 5)	2/5 (40.0%)	1/5 (20.0%)	3/5 (60.0%)	1/5 (20.0%)	2/5 (40.0%)	2/5 (60.0%)	2/5 (40.0%)	1/5 (20.0%)	3/5 (60.0%)	1/5 (20.0%)
PL-12 (n = 6)	1/5 (20.0%)	1/4 (14.3%)	4/6 (42.9%)	3/6 (50.0%)	1/1 (16.7%)	3/6 (50.0%)	5/6 (83.3%)	1/6 (16.7%)	3/6 (50.0%)	2/6 (33.3%)
EJ (n = 1)	0/1 (0%)	0/0 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	0/1 (0%)
OJ (n = 2)	1/2 (50.0%)	0/0 (0%)	1/1 (100%)	0/2 (0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)
Ku (n = 2)	2/2 (100%)	0/1 (0%)	2/2 (100%)	1/2 (50.0%)	0/2 (0%)	1/2 (50.0%)	2/2 (100%)	0/2 (0%)	1/2 (50.0%)	0/2 (0%)
NXP (n = 3)	3/3 (100%)	0/2 (0%)	1/2 (50.0%)	2/3 (66.7%)	0/3 (0%)	2/3 (66.7%)	3/3 (100.0%)	0/3 (0%)	1/3 (33.3%)	0/3 (0%)
TIF1g (n = 1)	1/1 (100%)	0/0 (0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	1/1 (50.0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
Pm/Scl (n = 4)	4/4 (100%)	2/2 (100%)	2/4 (50.0%)	3/4 (75.0%)	3/4 (75.0%)	4/4 (100%)	4/4 (100%)	2/4 (50.0%)	3/4 (75.0%)	0/4 (0%)
SRP (n = 2)	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	2/2 (100%)	0/2 (0%)	2/2 (100%)	0/2 (0%)
Mi2 (n = 5)	5/5 (100%)	0/1 (0%)	1/3 (33.3%)	5/5 (100%)	2/5 (40.0%)	5/5 (100.0%)	5/5 (10.0%)	1/5 (20%)	1/5 (20%)	3/5 (40%)

Abbreviations: ANA = anti-nuclear antibodies, RF = rheumatoid factor, GERD = gastroesophageal reflux disease.

<sup>a</sup> Clinical manifestations are reported if documented as ever present.

<sup>b</sup> Documented in a rheumatologist's note.

<sup>c</sup> These are non-overlapping phenotypes. All patients with anti-tRNA synthetase antibodies were categorized as anti-synthetase syndrome.



**Fig. 1.** Time to diagnosis for patients with ARS-ILD (n = 21) compared to DM/PM-ILD (n = 14). Mann-Whitney U-test shown.

age of UIP-pattern patients being older than non-UIP pattern patients (63.3, IQR 54.8,70.8 yrs, v. 55.2, IQR 46.8,60.6 yrs,  $p = 0.09$ ). Bronchiectasis trended towards being more prevalent in ARS compared to other IIM subsets (50% v. 22.2%,  $p = 0.10$ ). Of ARS patients, 13.6% had frank honeycombing, which was not seen in any other IIM subset. There was no difference in the frequency of ground glass abnormalities between ARS and other IIM patients.

### 3.5. Physiologic features of ARS-ILD

Physiologic features of IIM- and SSc-ILD are shown in Figs. 2 and 3. Due to the paucity of PM patients with ILD, these were again excluded from subgroup statistical analyses. Overall, patients with IIM and SSc had comparable restriction (60.3% v. 66.6% predicted FVC,  $p = 0.15$ ) and diffusion impairment (48.0% v. 51.1% predicted DLCO,  $p = 0.63$ ). However, ARS-ILD demonstrated more severe reduction in FVC (53.2% predicted) than patients with DM (66.9% predicted,  $p = 0.005$ ) or lcSSc (71.8% predicted,  $p = 0.005$ ). The severity of ARS- and dcSSc-ILD was comparable (53.2% v. 56.8% predicted FVC,  $p = 0.48$ ). Similarly, patients with ARS were more likely to have a severe diffusion impairment (e.g. <40% predicted) than in DM (59.0% v. 5.0%,  $p = 0.007$ ) but not dcSSc (59.0% v. 30.0%,  $p = 0.25$ ). While there was a trend towards worsening impairment of diffusion in ARS relative to DM (39.8% v. 48.0% predicted DLCO,  $p = 0.08$ ) and dcSSc (39.8% v. 51.4% predicted DLCO,  $p = 0.13$ ), this did not reach statistical significance. There was no difference in diffusion impairment for IIM-ILD patients with or without pulmonary hypertension. There was no difference in the severity of restriction or diffusion impairment ARS-ILD patients with positive vs. negative Jo-1 antibodies.

## 4. Discussion

Our primary findings can be summarized as following, (1) patients with ARS have a high frequency of interstitial lung disease with more severe restriction than other IIM subsets (2) only ARS-ILD patients in this cohort had CT reads of UIP, (3) patients with ARS are frequently referred



**Table 3**

Comprehensive myositis serologies play a critical role in the serologic detection of ARS-ILD compared to other IIM-ILD.

	+ANA	+RF	+CCP	Diagnostic yield after initial serologic work-up	Diagnostic yield after testing CK level	Diagnostic yield after adding MSA/MAA <sup>a</sup>
Dermatomyositis (n = 15)	11/12 (86.7%)	3/6 (50.0%)	2/4 (50.0%)	13/15 (86.7%)	13/15 (86.7%)	13/15 (86.7%)
Polymyositis (n = 3)	1/3 (33.3%)	1/3 (33.3%)	1/2 (50%)	1/3 (33.3%)	3/3 (100%)	3/3 (100%)
Anti-synthetase Syndrome (n = 22)	5/20 (25.0%)	4/18 (22.2%)	0/13 (0%)	7/21 (33.3%)	16/22 (72.7%)	22/22 (100%)

Abbreviations: ARS-ILD = anti-tRNA synthetase related interstitial lung disease, IIM-ILD idiopathic inflammatory myopathies associated interstitial lung disease, ANA = anti-nuclear antibodies, RF = rheumatoid factor, CCP = anti-cyclic citrullinated peptide, CK = creatinine kinase.

<sup>a</sup> MSA = myositis specific antibodies (Jo-1, PL-7, PL-12, OJ, EJ, Mi-2, SRP, TIF-1γ, MJ/NXP-2, SAE, MDA-5/CADM-140; MAA = myositis associated antibodies (Pm/Scl, Ku, U1RNP, U3RNP, Ro52).

**Table 4**

Radiographic features of interstitial lung disease in patients with IIM compared to SSC.

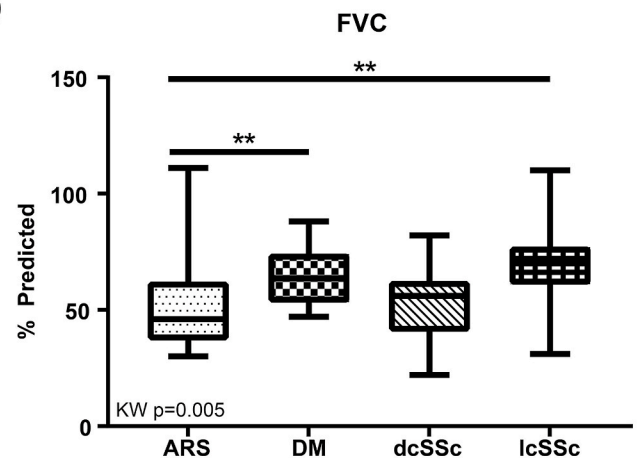
	Radiographic Characteristics			
	UIP	GGO	BC	HC
<b>Inflammatory Myositis</b>				
Dermatomyositis (n = 15)	1/13 (7.7%)	10/13 (76.9%)	4/13 (30.8%)	1/13 (7.7%)
Polymyositis (n = 3)	0/3 (0%)	2/3 (66.7%)	0/3 (0%)	0/3 (0%)
Anti-Synthetase Syndrome (n = 22)	5/22 (22.7%)	12/22 (54.5%)	11/22 (50%)	3/22 (13.6%)
<b>By Serology</b>				
Jo-1 (n = 10)	2/10 (20%)	9 (90%)	7/10 (70.0%)	12 (20.0%)
PL-7 (n = 5)	1 (20%)	3 (60%)	4 (80%)	3 (60%)
PL-12 (n = 5)	1 (20.0%)	4 (80%)	4 (80%)	1 (20%)
EJ (n = 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
OJ (n = 1)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Ku (n = 2)	0 (0%)	1/2 (50%)	0 (0%)	0 (0%)
NXP (n = 1)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
Pm/Scl (n = 3)	0 (0%)	3/3 (100%)	1/3 (33.3%)	0 (0%)
SRP (n = 1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mi2 (n = 1)	0 (0%)	1 (100%)	1 (100%)	0 (0%)
<b>Systemic Sclerosis</b>				
lcSSc (n = 18)	3/15 (20%)	9/15 (60%)	8/15 (53.3%)	5/15 (33.3%)
dcSSc (n = 10)	1/9 (11.1%)	8/9 (88.9%)	6/9 (66.7%)	5/9 (55.6%)

Abbreviations: IIM = idiopathic inflammatory myopathies, SSc = systemic sclerosis, UIP = usual interstitial pneumonia (definite or probable), GGO = ground glass opacities, BC = bronchiectasis, HC = honeycomb changes, lcSSc = limited cutaneous systemic sclerosis, dcSSc = diffuse cutaneous systemic sclerosis.

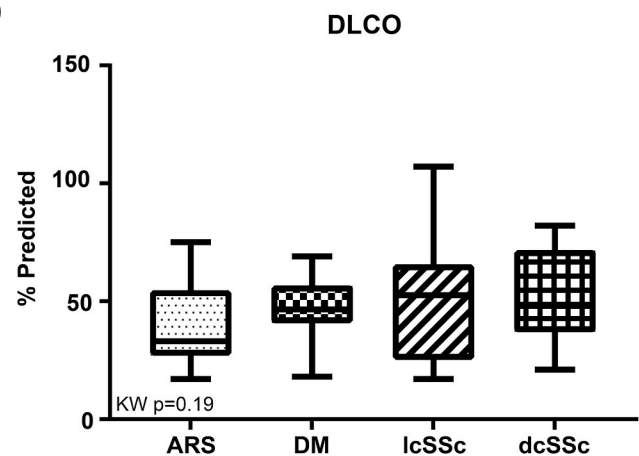
to a tertiary center after seeing a local pulmonologist and/or rheumatologist without receiving the correct diagnosis, and (4) patients with ARS-ILD have a delayed diagnosis compared to DM-ILD and PM-ILD.

Improving recognition of ARS-ILD is key to ensuring these patients have prompt access to immunosuppressive therapies. Diagnostic delays in ARS are well described and are known to be an independent risk factor for mortality in ARS-ILD [2]. Cavagna et al. described Jo-1 positive patients who presented without the classic triad of arthritis, myositis, and interstitial lung disease had a trend towards increased median time to diagnosis from 2.5 to 10 months [15]. While delays in ARS-ILD diagnosis are frequently discussed in the literature, to our

a)

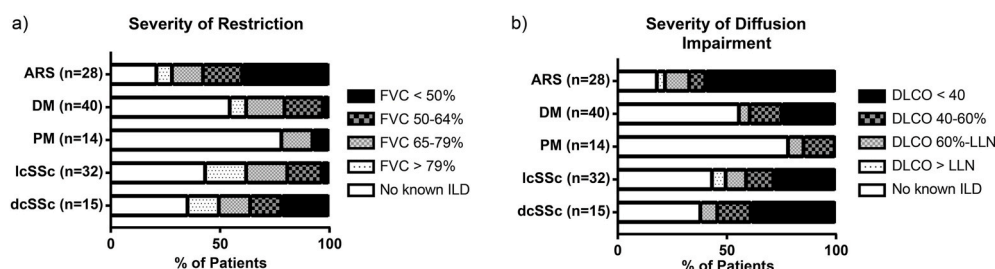


b)



**Fig. 2.** Physiologic features of IIM-ILD compared to SSc-ILD. (A) Patients with ARS have more severe restriction than DM or lcSSc and similar restriction compared to dcSSc. (B) There is no significant difference in diffusion impairment amongst IIM or SSc subsets. Box plots depict median  $\pm$  IQR, KW=Kruskal-Wallis, Mann-Whitney *U* test \**p* < 0.05, \*\**p* < 0.01.

knowledge this is the first report to quantify a delay in diagnosis in ARS-ILD compared to other IIM-ILD. Given that nearly 25% of ARS patients present first with ILD [2], decreasing the diagnostic delay is critical. In our cohort, patients with ARS were much less likely than DM patients to have a positive ANA, RF, or anti-CCP antibody or classical skin changes such as a heliotrope rash or Gottron's sign. ARS patients were also less likely than PM patients to have proximal muscle weakness. While we postulate these factors contributed to delayed recognition, we could not statistically evaluate this hypothesis.



**Fig. 3.** Stratification of physiologic impairment according to American Thoracic Society criteria. The severity of impairment of (A) FVC and (B) DLCO for IIM and SSc subsets are shown.

The frequency with which ARS-ILD presents with UIP radiographically further complicates recognition of ARS-ILD. In our cohort, 22.7% of patients had CT scans read as compatible with UIP. While ARS-UIP may be enriched at an academic center, it has previously been recognized that most IIM-UIP is associated with ARS. Of the 43 patients in the Pittsburgh cohort with biopsy proven UIP, only one did not have ARS [16]. Using the 2013 Fleischner Society guidelines, a cohort of 69 Chinese ARS-ILD patients identified that 8.7% had a high resolution CT scan classified as UIP [17]. A second longitudinal study of serial CT scans in ARS-ILD found that while 100% of patients had some ground glass at diagnosis, subsequent scans showed the ground glass decreased in 38%. Additionally, 42% of patients had honeycombing and 50% had worsening traction bronchiectasis at follow-up [18]. The prevalence of honeycombing and traction bronchiectasis in ARS may lead to radiographic classification as UIP on CT scans, especially in the community setting. The 2018 American Thoracic Society guidelines for diagnosing idiopathic pulmonary fibrosis allow patients with ground-glass opacities to be classified as UIP in the absence of other clear etiologies and so long as the ground-glass opacities are not the predominant radiographic feature [4]. Thus, ARS patients without prominent extra-pulmonary manifestations are at high risk for not being recognized as having an alternative etiology and miscategorized as UIP/IPF in the absence of comprehensive serologies.

In our cohort, only 33% of ARS patients were identified as having a CTD on basic screening serologies. While this is slightly lower than some prior studies [6,14,17], a substantial number of ARS patients are ANA, RF, and anti-CCP negative in all cohorts. Additionally, there is increasing evidence that obtaining comprehensive serologies and engaging rheumatology improves the care of ILD patients. Nakashima et al. evaluated the ARS serology status of 168 patients with idiopathic interstitial pneumonia and found that 10.7% were positive for an anti-tRNA synthetase antibody, including 5.3% of patients who were diagnosed as IPF [19]. Another study found that even a modest expansion of routine serologies and inclusion of a rheumatologist in the multi-disciplinary ILD team resulted in 21% of IPF patients being re-classified as having an autoimmune process and eight invasive diagnostic procedures were avoided [20]. This study further highlights the importance of using expanded serologies to aid in the identification of IIM-ILD generally and ARS-ILD specifically.

Prompt recognition of ARS-ILD is imperative as immunosuppression is efficacious in ARS-ILD. Previous work by Danoff and co-workers demonstrated that patients with IIM-ILD have an improvement in their FVC following treatment with immunosuppressive therapy [21]. A post-hoc analysis of the rituximab in myositis phase III clinical trial [22] indicated a benefit in ARS-ILD. Efficacy for tacrolimus in both naïve [23] and refractory IIM-ILD [24] has also been reported. Even patients with myositis-related UIP, which is nearly always ARS-ILD, have a slower rate of FVC decline and improved mortality compared with IPF patients after treatment with immunosuppression [16]. However, if a patient is not recognized to have ARS-ILD, they may not gain access to critically needed immunosuppressive agents. For this reason, we continue to advocate for the use of comprehensive serologies in the evaluation of

new patients with interstitial lung disease and the inclusion of rheumatologists as part of the multi-disciplinary team discussion of ILD patients.

One strength of this study is the inclusion of both a prospective longitudinal cohort and biorepository (MYSTIC) and electronic health record cohort (IAMC). These cohorts were combined to minimize bias. MYSTIC enrolls in both the rheumatology and pulmonary practices at Vanderbilt University Medical Center and is biased towards patients with ILD. IAMC is a cross-sectional cohort all rheumatology and pulmonary practices at VUMC that we created to ensure all phenotypes were represented in our analysis. This study also has several limitations. First, a cross-sectional design at a single center resulted in a limited sample size, which precluded comparisons between some IIM-ILD groups and ARS-ILD patients stratified by time to diagnosis. Second, not all CT scans used in this study were high-resolution, which is considered gold standard for the classification of ILD patterns. Additionally, since clinical CT reports were used from outside facilities, it is impossible to know what criteria were used in their determination, and it is unlikely that all reads were performed by a thoracic radiologist. Third, the use of retrospective chart abstractions meant that not all patients had a complete dataset, and data on objective muscle weakness across the entire clinical course was not available. While comprehensive myositis serologies are clearly useful for identifying ARS-ILD, the overall yield of comprehensive myositis screening in a tertiary ILD clinic is unclear.

## 5. Conclusions

ARS patients without prominent extra-pulmonary manifestations are at high risk for not being recognized as having an alternative etiology and miscategorized as UIP/IPF in the absence of comprehensive serologies. Future work is required to (1) quantify the benefit instituting comprehensive serologies and rheumatologic consultation in the care of ILD patients at a tertiary care center and (2) determine if obtaining comprehensive myositis serologies improves patient outcomes.

## CRedit authorship contribution statement

**Erin M. Wilfong:** Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft. **Jennifer J. Young-Glazer:** Data curation, Formal analysis, directly involved with patient care, Writing – review & editing. **Bret K. Sohn:** Conceptualization, Data curation, Formal analysis, directly involved with patient care, Writing – review & editing. **Gabriel Schroeder:** Data curation, Writing – review & editing. **Narender Annapureddy:** Data curation, directly involved with patient care, Writing – review & editing. **Erin A. Gillaspie:** Directly involved with patient care, Formal analysis, Writing – review & editing. **April Barnado:** Data curation, directly involved with patient care, Writing – review & editing. **Leslie J. Crofford:** Conceptualization, Project administration, directly involved with patient care, Writing – review & editing. **Rosemarie Beckford Dudenhofer:** Study conceptualization, directly involved with patient care, Writing – review &

editing.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2021.106432>.

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